BIVALENT BROMODOMAIN INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] The present application is a divisional of and claims priority under 35 U.S.C. § 120 to U.S. patent application U.S. Ser. No. 15/778,831, filed May 24, 2018, which is a national stage filing under 35 U.S.C. § 371 of International PCT Application, PCT/US2016/063502, filed Nov. 23, 2016, which claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Applications, U.S. Ser. No. 62/259,797, filed Nov. 25, 2015, U.S. Ser. No. 62/261,703, filed Dec. 1, 2016, and U.S. Ser. No. 62/338,968, filed May 19, 2016; the entire contents of each of which is incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant numbers U01 HD076508 and CA066996-01A1 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Cell-cell interactions and signal transduction often depend on multivalent interactions between receptors and their corresponding ligands (see, e.g., Mammen et al. *Angewandte Chemie International Edition* 1998, 37, 2754-2794). As is often the case in binding of carbohydrates (e.g., glycoproteins, glycolipids, polysaccharides, or proteoglycans) to lectins that have several binding sites, individual weak interactions can be enhanced more than 1,000-fold through multivalent interactions, a phenomenon known as the avidity effect (see, e.g., Monsigny et al. *Carbohydrate letters* 2000, 4, 35-52). Multivalent ligands that have either homo- or hetero-binding motifs show avidity by several mechanisms, such as interactions with oligomeric receptors, oligomerization of monomeric receptors, or increasing effective molarity of binding ligands (see, e.g., Kiessling et al. *Current opinion in chemical biology* 2000, 4, 696-703). Further, multivalent ligands can exhibit a prolonged residence time (see, e.g., Illendula et al. *Science* 2015, 347, 779-784). These historical observations from the natural world establish a strong rationale for multivalent ligand discovery (see, e.g., Profit, et al. *Journal of the American Chemical Society* 1999, 121, 280-283).

[0004] Molecular recognition of chromatin by transcriptional or epigenetic complexes is often mediated by proteins with single or multiple "reader" domains, which bind histone proteins, DNA, or transcription factors in specific post-translational modification states. In the context of transcriptional activation, recruitment of histone acetyltransferases leads to N-acetylation (Kac) of lysine residues on histone proteins and transcription factors. Local hyperacetylation leads to subsequent recruitment of co-activator proteins with acetyl-lysine recognition domains, or bromodomains. A bromodomain is an antiparallel bundle of alpha helices that recognizes mono- or di-acetylated peptides via a hydrophobic pocket with an adjacent, conserved asparagine residue (see, e.g., Filippakopoulos, P. & Knapp, S. *Nature reviews. Drug discovery* 2014, 13, 337-356). The BET (bromodomain and extra-terminal domain) family of human bromodomains are transcriptional co-activators involved in cell cycle progression, transcriptional activation and elongation (see, e.g., Zeng, L. & Zhou, M. M. *FEBS letters* 2002, 513, 124-128; Smith, S. G. & Zhou, M. M. *ACS Chem Biol* 2015, doi:10.1021/acschembio.5b00831). BET bromodomains (BRD2, BRD3, BRD4 and BRDT) are critical mediators of chromatin-dependent signal transduction from master regulatory transcription factors to RNA Polymerase II. BRD4, in particular, has emerged as a therapeutic target in cancer, as a co-activator protein for the prevalent oncoprotein, MYC (see, e.g., Zuber, J. et al. *Nature* 2011, 478, 524-528; Delmore, J. E. et al. *Cell* 2011, 146, 904-917). Further, BRD4 facilitates transcriptional elongation via recruitment or activation of the positive transcription elongation factor (P-TEFb) and displacement of negative regulators (HEXIM1 and 7SK snRNA) (see, e.g., Yang, Z. et al. *Molecular cell* 2005, 19, 535-545; Krueger et al. *PloS one* 2010, 5, e12335).

[0005] Recently, compounds have been reported to be bromodomain binding agents, e.g., international PCT publications WO 2015/013635, WO 2015/117083, WO 2015/117055, WO 2015/117053, WO 2015/117087, WO 2014/159392, WO 2014/195951, WO 2012/075383, WO 2011/054553, WO 2011/054841, WO 2011/054844, WO 2011/054845, WO 2011/054846, WO 2011/054848, WO 2011/143669, and WO 2011/161031, each of which is incorporated herein by reference. Moreover, Japanese patent application publication JP 2008/156311, incorporated herein by reference, discloses a benzimidazole derivative that is a BRD2 bromodomain binding agent and has been found useful in treating viral infections and inhibiting viral replication. International PCT publication WO 2009/084693, incorporated herein by reference, discloses a series of thienotriazolodiazepine derivatives that inhibit the binding between an acetylated histone and a bromodomain-containing protein which are useful as anti-cancer agents. International PCT publication WO 2011/054843, incorporated herein by reference, suggests compounds which inhibit the binding of a bromodomain with its cognate acetylated proteins may be useful in the treatment of autoimmune and inflammatory diseases.

[0006] The first direct-acting bromodomain antagonist, JQ1, was reported in 2010 (FIG. **1***a*) (see, e.g., Filippakopoulos et al. *Nature* 2010, 468, 1067-1073; WO 2011/143669). JQ1 is a potent and BET-selective thieno-1,4-diazepine which binds the critical asparagine via a methyltriazolo moiety. JQ1 has proven a valuable chemical probe for mechanistic and translational research, providing pharmacologic target validation in predictive models of solid tumors and hematological diseases. The structure of JQ1 is as follows:

(JQ1)